

**REMARKS**

Entry of the foregoing and further and favorable consideration of the subject application on the merits and in light of the following remarks are respectfully requested.

Claims 24-34 are currently pending. By this amendment, Claim 24 is amended for clarity, Claim 27 is amended to be an independent claim, and Claims 31-34 are canceled. Accordingly, no new matter is believed to have been added. For at least the reasons set forth herein, Applicants respectfully submit the application is now in condition for allowance.

1. Specification

The specification is objected to for failure to include the updated status of the parent application. By this amendment, the status of the parent application, now U.S. Patent 6,149,920, is indicated in the specification. Withdrawal of this objection is respectfully requested.

2. 35 U.S.C. §112, Second Paragraph

Claims 24-34 are rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite. Claim 24 is herein amended as suggested by the Examiner. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

## THE INVENTION

Before discussing substantive rejections, a review of the claimed invention is in order. The invention as claimed in independent claim 24 is directed to a method for immunization, prophylaxis or treatment of a vertebrate at risk of or suffering from a pathogenic micro-organism. The method comprises extracting deoxyribonucleic acid from the pathogenic micro-organism, identifying at least one gene encoding at least one antigen capable of stimulating protective immunity against the pathogenic micro-organism from the deoxyribonucleic acid, inserting the least one gene into a multicopy plasmid capable of replicating and expressing in the pathogenic micro-organism, transforming an attenuated or avirulent strain of the otherwise pathogenic micro-organism with the plasmid to form a vaccine, and administering an effective amount of the vaccine to the vertebrate. The resultant attenuated or avirulent strain of the micro-organism thus has at least two copies of the gene encoding the antigen which are susceptible to transcription and translation.

3. 35 U.S.C. §102(e)

Claims 24 and 25 are rejected under 35 U.S.C. §102(e) over Highlander *et al.* (U.S. Patent 6,180,112). For at least the following reasons, reconsideration and withdrawal of the rejection are respectfully requested.

Highlander is directed to compositions for the prevention of disease from *P. haemolytica*. In particular, Highlander is directed to the production of inactive leukotoxin for use in vaccines. The production of the inactive leukotoxin polypeptide is achieved through insertional inactivation of the lktC gene in *P. haemolytica*, and the addition of

leukotoxin polypeptide activators or promoters to the gene sequence. The addition of the activators or promoters for the leukotoxin polypeptide causes overproduction of the leukotoxin polypeptide.

In contrast to the claimed invention, over-expression in Highlander is achieved by adding one or more of an activator or promoter of the leukotoxin polypeptide to either the genome or an extrachromosomal element. See column 13, lines 2-5: "It is intended that the recombinant element may be present in the chromosome or maintained as an extrachromosomal element (e.g., as a plasmid)" (emphasis added). More importantly, the gene encoding the desired over-expressed product, leukotoxin polypeptide, is not itself duplicated in any manner. The invention as claimed in independent claim 24 requires that the over-expressed antigen be the result of transcription and translation of the gene encoding the antigen at least at two sites, the genome and the plasmid.

Thus, Highlander differs from the claimed invention in that Highlander does not disclose a method of immunization, prophylaxis or treatment of a vertebrate at risk of or suffering from a pathogenic micro-organism wherein the treatment includes administering a vaccine comprising an attenuated or avirulent strain of a pathogenic micro-organism transformed with a plasmid capable of replication and expression in the micro-organism, wherein the plasmid contains at least one gene identified from the deoxyribonucleic acid of the micro-organism and encoding at least one antigen capable of stimulating protective immunity against the micro-organism, resulting in transcription and translation of the gene encoding the antigen occurring at least at two sites, the genome and the plasmid. Therefore, Highlander does not disclose or suggest the subject matter of the claimed

invention. For at least the above reasons, reconsideration and withdrawal of the rejection are respectfully requested.

4. U.S.C. §103(a)

Claims 24-26, 31 and 33 are rejected under 35 U.S.C. §1-3(a) over Kontinen *et al.* (WO 94/19471) in view of Highlander *et al.* (U.S. Patent 6,180,112). Claims 31 and 33 are herein canceled without prejudice or disclaimer, making that portion of the rejection moot. With regard to the rejection of claims 24-26, for at least the following reasons, reconsideration and withdrawal of the rejection are in order.

Kontinen discloses an expression system for over-expressing homologous or heterologous exoproteins in gram-positive bacteria. The exoproteins may be from gram-positive bacteria, gram-negative bacteria, or other micro-organisms. The over-expression is achieved by inserting DNA constructs of the desired exoprotein into either the chromosome of the species used for expression, or into a plasmid inserted into the species.

In contrast to the claimed invention, and as admitted by the Patent Office at page 5 of the rejection, Kontinen does not disclose or suggest a method of immunization, prophylaxis or treatment herein the attenuated or avirulent strain of an otherwise pathogenic micro-organism is administered. Further, Kontinen over-expresses the PrsA protein of the bacterium and at least one exoprotein of interest. Neither the PrsA protein nor the exoprotein are indicated as capable of stimulating protective immunity against the bacterium expressing them. Thus, Kontinen does not disclose or suggest every feature of the claimed invention.

Highlander does not cure the deficiencies of Kontinen. As discussed above, Highlander does not disclose a method of immunization, prophylaxis or treatment of a vertebrate at risk of or suffering from a pathogenic micro-organism wherein the treatment includes administering a vaccine comprising an attenuated or a virulent strain of a pathogenic micro-organism transformed with a plasmid capable of replicating and expression in the micro-organism, wherein the plasmid contains at least one gene identified from the deoxyribonucleic acid of the micro-organism and encoding at least one antigen capable of stimulating protective immunity against the micro-organism, resulting in transcription and translation of the gene encoding the antigen occurring at least at two sites, the genome and the plasmid. Further, over-expression in Highlander is of the product, not the gene, and is achieved by adding one or more of an activator or promoter of the leukotoxin polypeptide. The gene encoding the desired over-expressed product, leukotoxin polypeptide, is not itself over-expressed in any manner. Thus, Highlander alone does not teach or suggest all of the features of the claimed invention.

Combining the teachings of Kontinen with Highlander does not result in the claimed invention because neither reference discloses or suggests that the protein or antigen encoded by an over-expressed homologous gene occurring both in the genome and a plasmid is capable of stimulating protective immunity against the micro-organism expressing it. That is, neither reference discloses or suggests over-expression of a homologous gene encoding an antigen which stimulates protective immunity against the micro-organism expressing the gene. Thus, neither reference, taken alone or in combination, discloses or suggests the

subject matter of the claimed invention. For at least these reasons, reconsideration and withdrawal of the rejection are respectfully requested.

5. 35 U.S.C. §112, first paragraph

Claims 31-34 are rejected under 35 U.S.C. §112, first paragraph, as allegedly not enabled by the specification. By this amendment, claims 31-34 are canceled without prejudice or disclaimer. Thus, the rejection is moot. Accordingly, withdrawal of this rejection is respectfully requested.

Applicants note no substantive rejection of claims 27-30 has been made by the Patent Office. Applicants herein amend claim 27 to an independent claim, from which claims 28-30 depend. Allowance of at least claims 27-30 is respectfully requested. In addition, for at least the above reasons, applicants submit that all of claims 24-26 are in condition for allowance. Claims 31-34 are canceled herein. Prompt reconsideration and response in the form of a Notice of Allowance regarding claims 24-30 is thus respectfully solicited.

*→ no claims 24-30 were rejected!*

Should the Examiner have any questions or require any further assistance, she is requested to contact Applicants' undersigned representative.

Respectfully submitted,

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**Attachment to Reply and Amendment dated July 29, 2002**

**Marked-up Copy**

**Page 1, Paragraph Beginning at Line 1**

This application is a divisional of Application No. 09/091,521, filed June 19, 1998,  
now U.S. Patent 6,149,920 issued November 21, 2000, which is a national stage  
application of PCT/US97/23032 filed December 5, 1997.

**Attachment to Reply and Amendment dated July 29, 2002**

**Marked-up Claims 24 and 27**

24. (Twice Amended) A method for immunization, prophylaxis or treatment of a vertebrate at risk of or suffering from a disease caused by a pathogenic micro-organism comprising the steps of:

- a) extracting deoxyribonucleic acid from the pathogenic micro-organism;
- b) identifying at least one gene encoding at least one antigen from the deoxyribonucleic acid, wherein said at least one antigen is capable of stimulating protective immunity against the pathogenic micro-organism;
- c) inserting the at least one gene into a multicopy plasmid capable of replicating and expressing in the pathogenic micro-organism;
- d) transforming an attenuated or avirulent strain of the otherwise pathogenic micro-organism with the plasmid to form a vaccine; and
- e) administering an effective amount of said vaccine to the vertebrate.

27. (Twice Amended) [The] A method [of claim 26,] for immunization, prophylaxis or treatment of a vertebrate at risk of or suffering from a disease caused by a pathogenic micro-organism comprising the steps of:

- a) extracting deoxyribonucleic acid from the pathogenic micro-organism;
- b) identifying at least one gene encoding at least one antigen from the deoxyribonucleic acid wherein said at least one antigen is capable of stimulating protective immunity against the pathogenic micro-organism;
- c) inserting the at least one gene into a multicopy plasmid capable of replicating and expressing in the pathogenic micro-organism;

**Attachment to Reply and Amendment dated July 29, 2002**

**Marked-up Claims 24 and 27**

d) transforming an attenuated or avirulent strain of the otherwise pathogenic micro-organism with the plasmid to form a vaccine; and

e) administering an effective amount of said vaccine to the vertebrate,

wherein the pathogenic micro-organism is *Brucella* selected from the group consisting of *B. abortus*, *B. melitensis*, *B. suis*, *B. ovis*, *B. neotomae* and *B. canis*.